THE TOXICITY OF HUMAN TONSILS.*

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The relation of the tonsils to diseases of other parts of the body is a much-discussed subject. Besides those affections in which the tonsils serve clearly as an atrium of infection, there are others in which the relationship is not so well understood. Among these, Kyle[1] emphasizes asthma. He considers this in the nature of a reflex neurosis but also considers the possibility of the absorption of toxic substances from the tonsils. Tschiassny[2] reports a case of recurrent bronchial asthma in which removal of the tonsils resulted in a cessation of the attacks. The frequency of convulsions in children and of so-called epileptiform attacks in young individuals with hyperplastic lymphadenoid systems has led to some speculation as to the relationship of this condition to such attacks. Here too the reflex and the toxic possibilities are those considered. Fignero[3] reports a case of epilepsy in a boy of 13 who had no further attacks during the period of four years following the removal of adenoids. The idea of absorption of toxic substances through the tonsils is supported by the changes of chronic tonsillitis. Davis[4] mentions the action of toxins as a possible explanation of the plasma cell infiltrations in tonsils.

The source of the supposed intoxication generally is said to be that of the bacteria associated with the tonsils. It is known, however, that the bacteria usually found in the tonsils do not form soluble toxins. Dold and Aoki[5] have succeeded in forming anaphylatoxin from streptococci which are the commonest organisms found in chronic tonsillitis, but only with some difficulty, while others have failed entirely. It is evident that while the assumption of absorp-

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[1] *Diseases of the Nose and Throat,* Philadelphia, 1909.

[2] *Monatschr. f. Ohrenheilk. u. Laryngo-Rhinolog.*, 1913, 47, p. 356.

[3] *Arch. de med. des enfants*, 1912, 15, p. 691.

[4] *Jour. Infect. Dis.*, 1912, 10, p. 147.

[5] *Ztschr. f. Immunitätsf.*, 1912, 13, p. 200.

tion of toxic substances from the tonsil is common, the problem of the existence and nature of the toxic substances is still unsolved. It would seem therefore that this subject is worthy of further investigation.

The work, the results of which we now report, was undertaken to determine first, whether or not there are toxic substances in the tonsils; second, if present, the nature of those substances, and third, the factors influencing the degree of toxicity.

The material was obtained from a series of 32 tonsillectomies.[1] The tonsils were received in sterile gauze. Extracts were then made by grinding them in a mortar with 10 c.c. of salt solution. The extract thus obtained was either centrifuged or filtered through paper and examined bacteriologically as follows: blood agar plates were made by adding one cubic centimeter of goat blood to seven to nine cubic centimeters of agar; the plates were allowed to harden, and one drop of extract to be examined was smeared over the surface of two plates by means of a platinum spatula; after incubating, 18–24 colonies were examined grossly and microscopically.

The following will serve as examples of these experiments:

A rabbit received two cubic centimeters of tonsillar extract intravenously (marginal veins of ear). After one and one-half minutes it urinated, jumped several times, fell on one side, jumped again, had clonic movements (opisthotonos), and died. Quivering contractions of muscles could be felt even after the animal lay on its side apparently dead. On examination 20 minutes later both ventricles were in contraction; the right muscle in rhythmic contractions, lungs not distended; no pulmonary hemorrhage, heart's blood fluid.

A guinea-pig received four cubic centimeters of extract intravenously. Temperature before, 102° F. Sneezing followed by convulsions within 30 seconds after injection, temperature after one and one-half minutes, 100.7° F.; respiration ceased after two and one-half minutes. Postmortem, typical pulmonary distensions with subpleural hemorrhages; heart contracting feebly but in rhythm, right ventricle slightly dilated; heart's blood fluid.

Female dog, weight 9 kilograms, received five cubic centimeters intravenously. Convulsions, urinated, defecated, vomited within two minutes, recovery within five minutes.

It was noted that of animals injected with toxic extracts the rabbit usually exhibited, besides the symptoms noted, a marked exophthalmos and contracted pupils. Postmortem examinations

[1] We wish to thank Dr. A. A. Hayden, of St. Joseph's Hospital, Chicago, for his courtesy in providing us with material.

were made in nearly all cases and the changes are all illustrated by the protocols given. In no instances were evidences of embolism or thrombosis found. The coagulation of the blood was delayed.

The extracts were prepared and injected in some cases immediately upon removal of the tonsils. A few of them were prepared after freezing the tonsils for 24 hours; most of them were made a few hours after removal. The toxicity was apparently not affected by these varying conditions.

It is evident from the protocols that the symptoms and changes in the animals resemble very much the conditions found in anaphylactic shock in rabbits,[1] guinea-pigs,[2] and dogs.[3]

Friedberger[4] found that anaphylatoxin was destroyed by heating to 65° C. Heating our extracts to 60°–65° C. diminished their toxicity markedly without, however, rendering them entirely harmless since a rabbit, which received two cubic centimeters intravenously, had convulsions within 30 seconds, and died within two minutes. The same quantity of the same extract, heated to 65° C., for 30 minutes, produced uneasiness after one minute, slight twitching after three minutes, mild convulsive movements after five minutes, and death.

The effect of passing of tonsillar extracts through Berkefeld filters was tried as follows: a rabbit, which received one cubic centimeter intravenously, had convulsions and died within one minute; a guinea-pig received one cubic centimeter intracardially and showed jerky respirations; a guinea-pig received one cubic centimeter of the Berkefeld filtrate intravenously and showed no symptoms.

Not infrequently, as is also illustrated by this result, it was found that some extracts which were fatal for rabbits were far less toxic for guinea-pigs.

Friedberger and Hartoch[5] have also shown that hypertonic salt solution previously injected protects animals against anaphylactic shock. Hypertonic salt solution also protects animals against the action of tonsil extracts. While two cubic centimeters of a

[1] Auer, *Jour. Exper. Med.*, 1911, 14, p. 476.

[2] Auer and Lewis, *Jour. Exper. Med.*, 1910, 12, p. 151.

[3] Schittenhelm and Weichardt, *München. med. Wchnschr.*, 1910, 58, p. 841.

[4] *Ztschr. f. Immunitätsf.*, 1910, 7, p. 751.

[5] *Ibid.*, 1909, 3, p. 587.

certain extract killed immediately, the injection of one and one-half cubic centimeters of 25 per cent NaCl solution intravenously caused a few clonic convulsions within one minute or so, followed by complete recovery, and protected fully against two cubic centimeters of tonsil extract given immediately after the convulsion.

Friedberger and Mita[1] found that by injecting slowly, twice the fatal dose of anaphylatoxin can be given. This is true of toxic extracts of tonsil also: a rabbit was injected at intervals of a few minutes with 0.5 c.c. doses. In all, six doses were given, a total of three cubic centimeters. The animal remained unaffected. The same extract injected immediately afterward into two animals in doses of one and one-half and two cubic centimeters proved rapidly fatal to both.

The protective inoculation of atropin in anaphylactic shock has been noted by various investigators, notably Auer,[2] and the effect of atropin with respect to toxic tonsillar extracts was tried as follows: a large rabbit was injected with three cubic centimeters of extract. Convulsions and death followed within four minutes. A much smaller rabbit was injected with three cubic centimeters four minutes after an intravenous injection of 0.02 of a grain of atropin. At the time of injection of extract the pupils were dilated. Within one minute the pupils contracted. The animal died without convulsions. The atropin, then, seemed to exert an antispasmodic effect but did not prevent death.

It seems clear that the extracts of tonsils contain a substance which manifests many of the characteristics of the so-called anaphylatoxin of Friedberger. In this connection the toxic extracts of normal organs investigated particularly by Dold[3] may be mentioned. He found that such extracts produced harm by causing coagulation of the blood and were easily affected by heat, thus differing from the extracts of tonsils.

A few tonsils were apparently harmless in the doses of extract used. A search for the underlying factors was made by comparing the toxicity with the bacterial flora, structural changes, and the amount of sediment, i.e., parenchyma, obtainable. The bacterial

[1] *Deutsch. med. Wchnschr.*, 1912, 38, p. 204.

[2] *Ztschr. f. Immunitätsf.*, 1912, 12, p. 235.

[3] *Ztschr. f. Immunitätsf.*, 1911, 10, p. 53.

TABLE 1.

Case	Toxicity c.c.		Predominating Bacteria	Bacteria Second in Number	Bacteria Third in Number	Bacteria Fourth in Number
1...	1	D	M. catarrhalis	Pneumococcus	Sta. albus	.....
2...	1	D	Hemolytic streptococci, large colonies, short chains	.....	.....	.....
3...	1 2 1.5 6	D	Hemolytic streptococci, large colonies	Hemolytic streptococci, punctate colonies very few	.....	.....
4...	0.5	D	Str. viridans	Sta. albus	Many punctate hemolytic streptococci	.....
5...	2.5	D	Hemolytic streptococci, large colonies	Str. viridans	Sta. albus	.....
6...	1.5	D	Hemolytic streptococcus, large colonies	Hemolytic streptococcus, punctate colonies	.....	.....
7...	3	D	Str. viridans	Many hemolytic streptococci, punctate colonies	M. catarrhalis	Pneumococcus
8...	2 5 7	D	Pneumococcus	M. catarrhalis	Str. viridans	.....
9...	6	L	Pneumococcus	Str. viridans	.....	.....
10...	7	L	Str. viridans	Pneumococcus	.....	.....
11...	6	L	Hemolytic streptococcus, flat wrinkled colonies	.....	.....	.....
12...	2	D	Str. viridans	Sta. albus	Hemolytic streptococcus	.....
13...	2.5	D	Hemolytic streptococcus	Str. viridans	Sta. albus	.....
14...	1	D	Hemolytic streptococcus	Str. viridans	.....	.....
15...	6	L	Str. viridans	Friedländer's bacillus	.....	.....
16...	1	L C	Hemolytic streptococcus	Sta. albus	.....	.....
17...	1.5	D	Pneumococcus	Hemolytic streptococcus	M. catarrhalis	.....
18...	2	D	Pleomorphic gram-organism	Staphylococcus, small colonies	.....	.....
19...	6	L	Str. viridans	Pneumococcus	Sta. albus	Gram and diplococcus, no effect on blood
20...	2	D	Hemolytic staphylococcus	Pneumococcus	.....	.....
21...	7	L	Pneumococcus	Pseudodiphtheria bacillus	Str. viridans	Friedländer's bacillus
22...	2.5	L C	Hemolytic streptococcus	Pneumococcus	.....	.....
23...	1	D	Pneumococcus	Hemolytic staphylococcus	.....	.....

TABLE 1.—*Continued.*

Case	Toxicity c.c.		Predominating Bacteria	Bacteria Second in Number	Bacteria Third in Number	Bacteria Fourth in Number
24...	1	D	Hemolytic streptococcus, small colonies	Pneumococcus	.....	.....
25...	2	D	Str. viridans	Pneumococcus	M. tetragena	Friedländer's bacillus
26...	2	D	Hemolytic staphylococcus	Streptococcus, no effect on blood	.....	.....
27...	1	D	M. catarrhalis	Hemolytic streptococci, small colonies	.....	.....
28...	2	D	Pleomorphic gram-diplococcus	Hemolytic streptococcus	Pneumococcus	.....
29...	7	L	Hemolytic streptococci, large colonies wrinkled	Large diplococcus	Str. viridans	.....
30...	7	L	Streptococcus, large, flat, wrinkled colonies	Pneumococcus	Streptococcus, small hemolytic colonies	.....
31...	5	C dog	Hemolytic streptococcus, small punctate colonies	M. tetragena	.....	.....
32...	2	D	Plates	Contaminated	.....	.....
33...	5	L	Streptococci, no effect on blood	M. catarrhalis	Str. viridans	.....

D indicates death following injection; L indicates that the animal lived; C, convulsions.

flora was the only factor that seemed to bear any relationship to the toxicity of the extract. Space will therefore be given to a consideration of the bacteriology only. An idea of the connection between bacteria and toxicity can best be obtained from Table 1.

In the 10 cases in which relatively non-toxic extracts were obtained there was only one in which typical punctate hemolytic streptococcus colonies were present. In the remaining 23, from which highly toxic extracts were obtained, punctate, hemolytic, streptococcus colonies occurred 15 times in large numbers. In three additional cases large colonies of hemolytic streptococci were found. In the remaining five a hemolytic staphylococcus was found three times. Hence the toxic extracts were usually obtained when typical hemolytic streptococci were found on the plates in large or predominating numbers.

As previously stated, investigation has shown that anaphylatoxin is obtained with difficulty from streptococci; indeed Aronson[1]

[1] *Berl. klin. Wchnschr.*, 1912, 49, p. 204.

maintains that they never yield an acutely fatal toxin. The prevalence of these organisms in our most toxic extracts led us to an attempt to obtain anaphylatoxin from the organisms grown on the plates by the method of Friedberger. In only one out of six attempts was a toxic substance obtained. It would therefore seem that if these substances are formed from the bacteria present, then the tonsils must present conditions very favorable to their formation.

CONCLUSIONS.

1. Extracts of tonsils are acutely toxic for animals.

2. These substances affect animals in a manner similar to that of anaphylatoxin.

3. The relation of the toxicity of tonsil extracts to the bacterial flora demands further study. The results of this work, however, would indicate that as a rule extracts of those tonsils are most toxic which are associated with hemolytic streptococci.